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Medical Progress

Disaccharidase Deficiency in Health and Disease

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DISACCHARIDE INTOLERANCE with subsequent "fermentative diarrhea" was reported in the early literature, but was considered to be primarily of a temporary nature and limited to the pediatric group.[1] More than 50 years ago Starling[2] observed that the hydrolytic activity of the intestinal juice is inadequate to account for the rate of disappearance of disaccharides from the lumen. In 1935 Cajori[3] demonstrated this process more clearly in dog studies, but it remained for Borkström and Dahlqvist[4] in 1957 to clearly localize the hydrolysis to the intracellular portion of the intestinal tract. Following this observation, the first clinical application was made in 1958 with the report of intestinal lactase deficiency in humans.[5]

Since then the scope of this problem has been enlarging rapidly each year. New ramifications vary from foreign aid grants of dairy products to under-developed countries[6] with high lactase-deficiency rates to the treatment of osteoporosis.[7] It must be remembered that most of man's caloric needs are supplied by carbohydrates. In regions of low living standards, up to 80 percent of the total caloric intake is in carbohydrate form. Even in countries with high standards of living, about 50 percent of the dietary calories are obtained from carbohydrates. The chief dietary carbohydrates are the polysaccharide, starch, and the disaccharides, sucrose and lactose. The more important food sources of each of these complex carbohydrates has been reviewed by Harding et al.[8]

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Specificity of Intestinal Disaccharidases

The existence of several different α-glucosidases has been demonstrated in extracts of intestinal mucosa.[9-19] These enzymes have varying specificity for disaccharides with α-D-glucopyranoside structure (for example, maltose, sucrose, isomaltose, trehalose), and thus the intestinal hydrolysis of these sugars is caused by a complicated enzyme mixture.

The β-glucosidase and β-galactosidase activities of extracts of intestinal mucosa seem to be exerted by three enzymes, of which only two are lactases,[16-21] and only one has significant lactase activity at the usual intestinal pH of 5.8.[20]

Dahlqvist pioneered in the separation of the disaccharidases of the intestinal mucosa. He characterized them first in hog mucosa[11] and then in human intestinal mucosa obtained from surgical specimens.[17] He separated the enzymes by selective heat inactivation; other investigators added gel filtration chromatography.[18,19] Using different methods of separation and characterization, the group in Sweden[17] and the group in Zürich[18,19] have arrived at slightly different classifications for the enzymes (Table 1).

Gray,[20,21] using density gradient centrifugation, found three β-galactosidases, all having different molecular size, enzyme I being the largest and enzyme III the smallest. Of the three β-galactosidases in human intestine only I and II are ca-

TABLE 1.—*Specificity of the Human Intestinal Disaccharidases*[17-19]

Enzyme and Substrates		*Percentage of Total Activity Against Each Substrate*
Nomenclature of Semenza and Auricchio[18,19]	Nomenclature of Dahlqvist[17]	
Maltase 1	Maltase III	
	Maltose	10
Maltase 2	Maltase II	
	Maltose	15
Maltase 3 = Sucrase 1		
	Maltase I b = Sucrase	
Maltase 4 = Sucrase 2	Maltose	25
	Sucrose	100
Maltase 5 = Isomaltase = Palatinase	Maltase I a = Isomaltase = Palatinase	
	Maltose	50
	Isomaltose	100
Lactase 1 = Cellobiase 1 = Gentiobiase 1	= Cellobiase	
	Lactase	
Lactase 2 = Cellobiase 2 = Gentiobiase 2	= Gentiobiase	
	Lactose	100
	Cellobiose	100
Trehalase	Trehalase	
	Trehalose	100
Order of appearance on elution from Sephadex G 200 column	Order of increasing heat stability	

pable of splitting lactose, but since enzyme I is peculiar to intestine, has maximum specificity for lactose rather than other β-galactosides and has a pH optimum close to that of intraluminal intestinal fluids, it is quite likely that it is the enzyme responsible for digestion of dietary lactose. The fact that both human liver and kidney contain an enzyme that appears identical with intestinal enzyme II suggests that this is a ubiquitous enzyme perhaps localized in lysosomes. The physiological role of enzyme II is unknown, but human liver β-galactosidase has recently been shown to be deficient in patients with generalized gangliosidosis,[22] and liver homogenates from such patients are unable to release galactose from a monosialoganglioside. It is doubtful that it plays any significant role in lactose hydrolysis, since intact disaccharide appears incapable of quantitatively entering the absorptive cell[23-25] from either the intestinal or vascular side.

Gray[21] found that infants have the same constituent β-galactosidases as adults. This is not consistent with the suggestion by Huang and Bayless[26] that there is an "infantile" enzyme that wanes during childhood and an "adult" enzyme that develops later in life. Rather it is probable that man is born with a full complement of intestinal β-galactosidases, two of which are lactases.

Elliott et al[27] found two lactase enzymes in ten European children while lactase from nine full-blood aboriginal children consisted of only small amounts of enzyme I. The aboriginal children were lactose intolerant.

Development of Intestinal Disaccharidases

All of the intestinal disaccharidases are already active in the three-month-old human embryo.[28] The α-disaccharidase activities reach the normal adult level in the sixth to seventh month of fetal life. The only exception is maltase I, which is still low in the newborn. In most animals studied, the α-disaccharidase activities are still absent or very low at birth.[29-32] The β-disaccharidase activities reach their maximum in humans toward the end of fetal life. In the adult, the lactase values are occasionally reduced but still sufficient for hydrolysis of a normal lactose in-

take.[33,35] In animals, the lactase activity develops early in fetal life and drops to very low values (10 percent) in the young animal after weaning.[32,34]

In human studies[36] of populations with a high incidence of lactase deficiency lactase levels decrease following the weaning period and the adult levels are usually reached by 10 years of age. This time interval is extended a few years with higher milk ingestion.

Distribution of Disaccharidases

The finding that disaccharide hydrolysis occurs in the mucosa has naturally led to curiosity about where in the mucosal cells these enzymes are located.

Tissue fractionation has been used by Miller and Crane[37,38] for the isolation of brush border membranes from the epithelial cells of hamster small intestine. The disaccharidase activities are recovered in high yield in these brush border preparations.

Experiments based on incubation with slices of everted intestine *in vitro* have in most cases been performed with sucrose as the substrate. If a piece of surviving intestine is incubated *in vitro* with a mixture of glucose and fructose, glucose is rapidly absorbed and accumulated in the tissue while fructose is slowly absorbed and does not accumulate. If the intestine is incubated with sucrose, one also finds that glucose is accumulated in the tissue in large amounts while most of the fructose liberated is recovered from the incubation medium.[39]

In other experiments glucose oxidase has been included in the incubation medium.[39] This enzyme does not react with sucrose, but it rapidly oxidizes free glucose to gluconic acid which is not actively absorbed by the intestine. If the invertase were located on the surface of the mucosal cells in direct contact with the incubation medium, the glucose liberated on hydrolysis of sucrose would have become trapped by the glucose oxidase. This did not occur; the accumulation of intracellular glucose during incubation with sucrose plus glucose oxidase was as large as on incubation with sucrose alone.

Another group of investigators found that glucose liberated from maltose is trapped by glucose oxidase under similar conditions.[42] This may mean that at least one of the maltose splitting enzymes is actually located on the surface of the cell.

Most tissue incubation experiments thus indicate a superficial localization of the disaccharidases, and at least the invertase is not located in direct contact with the medium but rather is located inside some kind of surface membrane.[39-41]

Ugolev,[43] however, has evidence for a sucrase enzyme on the outside of a membrane. This concept is also in keeping with the finding that the molecular diameter of the disaccharides is too large to penetrate the cell membrane, while the enzyme could more rapidly pass out through the cell membrane.

Histochemical staining using synthetic substrates of glycosidase activities was originally described by Seligman et al.[44] A histochemical staining method utilizing disaccharides as substrates was developed by Dahlqvist.[45,46] Due to the slow reaction considerable autolysis occurred and made the localization of the stain uncertain, especially in the brush border. Jos et al[47] in Paris developed a much more sophisticated and superior modification of the disaccharidase activity staining method. With this method, the more intense staining is in the brush border and in the distal part of the villi. Similar observations have been made for other enzymes, such as alkaline phosphatase, non-specific esterase, and leucine aminopeptidase.[48] It has been argued,[49] however, that this distribution of the stain for an enzyme activity need not mean that the enzyme is more active in the distal parts of the villi, but may be a reflection of membrane damages in this part of the tissue which cause an increased accessibility of the staining reagents for the enzyme stained.

Studies on isolated brush borders of hamster intestine[50] with electron microscopy demonstrated 60-angstrom knobs attached to the lumen surface of the plasma membrane. Separation and recovery of the knobs and the plasma membrane are possible. The activities of the disaccharidases invertase and maltase reside in the knobs and are not found with the plasma membrane. These findings have not been confirmed in humans.

Dahlqvist devised a method for assay of intestinal disaccharidases[51,52] which is easy to use and has close reproducibility in various laboratories.[53-58] There is good correlation between enzyme levels and disaccharide intolerance tests if the biopsy specimen is obtained at the ligament of Treitz or beyond.

Intestinal disaccharidases in human sub-

jects[33,57,61] with a variety of disorders were assayed in surgical and peroral biopsy specimens from the duodenum, jejunum, and ileum. There was practically no activity in the first portion of the duodenum, but the disaccharidases then gradually increased to maximal activity in the first part of the jejunum and remained constant into the proximal ileum, but decreased in the distal ileum to 50 to 75 percent of the maximal activity. The sucrase to lactase (S/L) ratio[60,61] was stable along the entire intestine. In the lactase-deficiency subjects the decrease in enzyme persisted along the entire intestine. No disaccharidase activity was found in the stomach or colon, but small amounts of maltase activity[59] have been noted in kidney, and, to a lesser extent, brain, pancreas, and liver.

It has been observed[60] that the specific activity of disaccharidases obtained at operations are only about one-half of those obtained with peroral biopsy. The S/L ratio, however, is almost identical between the groups. Since there is such low disaccharidase activity in the proximal duodenum, the ratio of S/L or of maltase to lactase in a single specimen can be helpful in the identification of lactase deficiency. These ratios in the lactase-deficient group do not overlap those in the normal groups.[57,58,61,75] The S/L ratio was less than 4 to 1 in normal subjects and greater than 4 to 1 in lactase-deficient subjects.

Hydrolysis and Absorption of Disaccharides

In contrast to the rapid hydrolysis and absorption rates for sucrose and maltose in normal subjects,[62-66,68] lactose hydrolysis occurs at rates that are only about half of those for the other disaccharides so that absorption rates for the glucose and galactose products are appreciably below those found when the equivalent monosaccharide mixture is infused. This suggests that the hydrolysis step is rate-limiting in the overall process of lactose hydrolysis-monosaccharide absorption, whereas hydrolysis is apparently not the rate-limiting step for sucrose or maltose absorption.[62,63]

These studies are compatible with *in vitro* assays of human intestinal homogenates which show lactase to be only 50 percent of sucrase activity.[51]

Considering the relatively slow lactose absorption in normal subjects, the rise in blood sugar concentration after lactose ingestion cannot be expected to be comparable to that found after ingestion of other sugars. Indeed, these findings may explain the fact that about 20 percent of persons with normal intestinal lactase activity show little increase in blood sugar after ingestion of lactose.[67]

Lactase activity is inhibited[10,69] by a variety of monosaccharides. Lactase is inhibited by all three major dietary sugars—glucose, galactose, and fructose. However, sucrase and maltase are most inhibited by hydrolytic products of their natural substrate. Inhibition is maximal at pH 6.0, the pH normally found in the upper intestine.[70,72]

Monosaccharide inhibition of lactase may be of some physiologic importance. This suggestion is supported by the fact that after a standard meal the concentration of glucose in the jejunal lumen is about 20 to 40 mM,[71] a concentration in the same range as the K_i for glucose.

London et al,[24] using ^{14}C lactose, failed to resolve the question of whether in mammalian intestinal mucosal cells there is a β-galactoside permease as well as a β-galactoside hydrolase. In lactase-deficient and normal subjects there was no evidence that lactose may be taken into the cell against a concentration gradient. A permease lack would explain the temporary sugar intolerance seen in children who still retain normal disaccharides activity.[92]

Almost 50 percent of patients with osteoporosis have a deficiency of the intestinal enzyme lactase.[73] To check on this observed relationship, Condon et al[7] did calcium studies in lactase-deficient subjects. When lactose was administered orally in quantities sufficient to cause mild diarrhea, fecal calcium and fat increased and calcium balance became negative. However, in American Negroes the incidence of intestinal lactase deficiency is high, but the incidence of osteoporosis is low,[73] and in this instance there is no association between lactose intolerance and osteoporosis.

Drug absorption[74] was decreased slightly when diarrhea was induced either with lactose or with saline cathartics in lactase-deficient subjects. Also, it has been reported that lactose is a frequent filler in pharmaceuticals, so it may cause diarrhea and malabsorption on this basis[75] in lactase-deficient patients.

Pathophysiology and Symptomatology

If one or more disaccharidase enzymes are deficient, the corresponding disaccharides are not hydrolyzed and remain in the intestinal lumen.[72] In part, they are excreted unchanged in the feces, causing osmotic diarrhea, and in part they undergo bacterial degradation, causing fermentative diarrhea. Diarrhea is therefore the leading symptom of disaccharide malabsorption.[76-80] The degree of diarrhea depends on the irritableness of the bowel and the dose of the sugar. The abdomen is distended and usually vaguely painful. The distention at first is due to liquid in the small intestine and later to gas in the colon as the sugar reaches the bacteria. Borborygmi are prominent at all levels and flatulence appears with the loose stools. The stools are liquid, foamy, and have a typical acid smell. They contain large amounts of carbohydrates and low molecular weight fatty acids, products of the bacterial degradation of the nonabsorbed disaccharides.[81] Among these fatty acids, lactic acid is of special interest because it can easily be determined with chemical[82] or enzymatic methods.[83] It is present in normal feces only in traces and is found in large amounts in fermentative stools.[81] Steatorrhea, however, is a rare occurrence.[84]

Launiala, studying human subjects,[85] found that unabsorbed disaccharide in the proximal part of the small intestine causes pronounced movement of water and electrolytes into the lumen until the contents are in osmotic equilibrium with the extracellular fluid. The unabsorbed disaccharide contributes only about a third of the osomotic activity after osmotic equilibrium is reached.

In the colon, part of the disaccharide disappears through bacterial fermentation. Although there is absorption of water and electrolytes even in relative excess of substrate disappearance, enough fluid remains to give diarrheal stools.

The diarrhea is thus due to the osmotic activity of the disaccharide in the intestine together with the organism's tendency to Na^+-equilibrium between the intraluminal and extracellular fluids. There is no evidence to suggest that the bacterial fermentation of the disaccharide in the colon has an etiologic role in the diarrhea through decreased water absorption by the colon.

Weijers and his co-workers[81] assumed that the volatile organic acids, and possibly other metabolities of the bacterial flora, irritate the intestine, causing increased peristalsis, excretion of fluid and formation of mucus with subsequent diarrhea. Studies[86] using lactic acid infused via intestinal tube have not confirmed this as a mechanism of great importance.

Clinical Syndromes

Gastrointestinal symptoms due to food intolerance represent a large heterogeneous group of disorders lumped together. True food allergy and nonspecific causes may account for a large segment of the adult syndromes, but will not be reviewed. The clinical syndromes of monosaccharide and disaccharide malabsorption recognized at the present are listed in Table 2.

A. *Congenital (primary) syndromes*

1. Congenital lactose malabsorption without lactosuria (Holzel syndrome).

Lactose malabsorption due to congenital deficiency of lactase I was discovered in 1959.[87] Intestinal lactase activity is about 10 percent of normal. Symptoms (vomiting, chronic diarrhea) begin within the first few days of life when milk is the infants' only nutrition. Even severely malnourished infants with lactase deficiency will be cured when lactose is eliminated from the diet.[88]

2. Congenital lactose intolerance with lactosuria (Durand syndrome).

This more severe form of lactose intolerance was described in 1958.[5] Onset of symptoms is also within the first few days of life. In addition to vomiting and chronic diarrhea, the infants present with massive lactosuria, and in the majority of cases with albuminuria, aminoaciduria and renal acidosis. Blood glucose curves after a lactose load are somewhat diminished, but do not show the flat type of curve seen in lactose malabsorption without lactosuria. Despite elimination of milk from the diet about half of the infants eventually die. Autopsy shows changes in kidney, liver and central nervous system. It has been suggested that this may be due to a deficiency of lactase II, an enzyme present within the whole cell and not localized in the brush border.[89] Intact lactose is believed to be toxic, especially on the kidneys, where it is excreted and therefore concentrated (osmotic nephrosis). Milk has to be excluded from the diet early in life before irreparable damage has occurred. The pathogenesis of this syndrome has to be further

TABLE 2.—*Disaccharide Malabsorption Syndrome*

A. *Congenital (primary) syndrome*
   1. Congenital lactose malabsorption without lactosuria (Holzel syndrome)[87]
   2. Congenital lactose intolerance with lactosuria (Durand syndrome)[5,90,91]
   3. Congenital sucrose-isomaltose malabsorption[93–127]
   4. Congenital glucose-galactose malabsorption[130,131]

B. *Acquired (probably primary) syndromes*
   1. Acquired lactose malabsorption in the adult[123–361]

C. *Symptomatic (secondary) syndromes (all enzymes decreased)*
   1. Primary malabsorption syndromes (celiac disease,[55,189,190] idiopathic sprue,[53,55,173] tropical sprue)[55,62,191]
   2. Secondary malabsorption syndromes (Whipple's disease,[192] intestinal lymphoma,[55] intestinal lymphangiectasia,[53,192] abetalipoproteinemia)[53]
   3. Blind loop syndrome[53]
   4. Kwashiorkor[193]
   5. Infectious or nonspecific diarrhea in childhood[197–200] (acute gastroenteritis or enterocolitis)
   6. Severe malnutrition in infancy[194]
   7. Neomycin administration (only lactase studied)[195]
   8. Conovid therapy[196]

D. *Chance combination of acquired lactase deficiency with other gastrointestinal disease*
   1. Peptic ulcer[58]
   2. Partial gastrectomy[201–206]
   3. Ulcerative colitis[207–210]
   4. Regional enteritis[210,211]
   5. Irritable colon syndrome[212–216]
   6. Diverticulosis and diverticulitis of the colon[217]
   7. Infectious or nonspecific diarrhea in adults[55]
   8. Massive infestation with Giardia lamblia[86]
   9. Mucoviscidosis (cystic fibrosis of the pancreas)[218,219]
   10. Infectious hepatitis[55]

E. *Disaccharide malabsorption with intact enzyme concentration*
   1. Extensive small bowel resection[84]
   2. Physiologic diarrhea of breast-fed newborn[28]

F. *Suggested disease associations*[86]
   1. Ulcerative colitis
   2. Regional enteritis
   3. Irritable-colon syndrome
   4. Osteoporosis

investigated, but several family studies suggest an inborn error of metabolism transmitted as an autosomal recessive trait.[90,91]

Berg et al[92] reported one patient with typical clinical signs and symptoms and lactose intolerance with normal intestinal disaccharidases at 6 and 20 weeks of age. They suggested that a defect in the gastric mucosa, allowing disaccharide absorption from the stomach, would best explain these observations.

3. Congenital malabsorption of sucrose and isomaltose.

The malabsorption of sucrose and isomaltose was first described as a simple sucrose malabsorption by Weijers et al in 1960.[81] In the following years, the accompanying malabsorption of isomaltose was demonstrated by Prader's group.[93] Sucrase-isomaltase deficiency is an uncommon heritable disorder which has been noted mostly among children[81,93-120] and in only ten adults.[120-127] Less than half of the reported cases have been diagnosed by enzyme assay.[114-124,127] Eight of the 27 well-documented cases of sucrase deficiency have been found in family clusters. The disorder is present at birth. It is characterized by the appearance of fermentative diarrhea as soon as the ingested food contains sucrose, dextrins or starch. Dextrins and starch are badly tolerated because of their isomaltose content. As long as the newborn infant is fed human milk, there are no symptoms. When cow's milk, with the addition of sucrose or a mixture of dextrins and maltose, is given, diarrhea appears and the child stops gaining weight and fails to thrive. The elimination of sucrose, dextrins and starch from the diet is regularly followed by a quick improvement. Instead of eliminating sucrose one can, with the same good result, add sucrase (invertase) to each feeding.[81,127]

The symptoms vary in degree from individual to individual but are usually more severe in infants and young children than in older children and adults. They are, of course, also dependent on the amount of the ingested nonabsorbable disaccharides. A few patients manifest malabsorption of fat and xylose.[107] This complication disappears as soon as sucrose and isomaltose are eliminated from the diet. It may be caused by the accelerated intestinal passage,[60] or by the inhibiting effect of disaccharides on fat absorption.[128,129] With one exception,[105] the intestinal mucosa was always found to be histologically normal.[114-124,127] In the one exception (mucosal atrophy) the histologic features reverted to normal under treatment with a sucrose-free diet.[105]

The deficiency of more than one enzyme is un-

usual in an inborn error of metabolism. The following four explanations can be proposed:[60] The mutation may have affected a regulator gene which controls the synthesis of several enzymes; it may have affected the structural gene of a polypeptide chain which is common to several enzymes; different activities may be due to different active centers of the same enzyme molecule;[105] or, finally, there may be a common inhibitor of several enzymes.

There is little doubt that the disorder is hereditary. There are ten records of affected siblings[107] and two of consanguineous parents.[105,120] The finding of intestinal mucosal sucrase levels in the "low normal" range in relatives of two patients[127] suggested that heterozygotic individuals might have intermediate levels of the enzyme. Six pedigrees[119,127] indicated a recessive pattern of inheritance. The highly significant difference in the means of the sucrase-to-lactase ratios between 101 normal persons and the family members of all six probands makes a strong claim in using this ratio to identify heterozygotic carriers. The frequency of heterozygotic persons in the population sample was 8.9 percent. Assuming a representative sample and a recessive pattern of inheritance the frequency of the homozygotic deficiency state was estimated to be 0.2 percent—that is, almost half-a-million people in the United States would have sucrase deficiency.[127] Reports to date have not borne out this prediction.

4. Congenital glucose-galactose malabsorption.

This disorder, discovered in 1962[130] has so far been found in only eight cases.[86,130,131] Symptoms are identical to the disaccharide malabsorption syndromes and start soon after birth. Tolerance tests with glucose or with galactose reveal a flat response and induce diarrhea. Because glucose is the constituent monosaccharide of all disaccharides, all disaccharide tolerance tests are also abnormal. The only tolerated carbohydrate is fructose, which renders alimentation difficult. Glucose and galactose are the only actively absorbed monosaccharides.[72] Active absorption requires energy. It involves a carrier system and probably one or several enzymes. The exact mechanism of normal glucose-galactose active transport has not yet been elucidated[72] and the basic defect in glucose-galactose malabsorption therefore not yet found.

B. *Acquired (probably primary) syndromes*

1. Acquired lactase deficiency in the adult.

When milk intolerance secondary to isolated lactase deficiency was first described in apparently healthy adults, it was thought to be a residual of some ill-defined, transient injury or inflammation of the gastrointestinal tract.[2] Then, in 1966, independent studies, in the United States[132] and in Africa,[146] demonstrated a racial difference between blacks and whites in the incidence of isolated lactase deficiency. Current evidence indicates that low lactase levels are the norm in the majority of adults in most populations of the world.[143-167] Notable exceptions[132-142] are Scandinavians and those of Northern European extraction (Table 3). Adults with low lactase levels were able to drink milk as infants. Environmental factors, such as malnutrition, parasitosis, infectious diarrhea with the resultant mucosal damage, along with decreased milk ingestion might hasten the appearance of lactose intolerance. Conversely, maintenance of an adequate nutritional status by continued milk ingestion and the avoidance of intestinal damage during early childhood might delay, for a few years, the apparent onset of inadequate lactose digestion.[36,168,169] A few investigators[157,163] interpret this maintenance of lactase activity for three or four years as induction of enzyme activity by the presence of substrate. In any event, at the end of the first or second decade of life, lactase levels are deficient in most members of population groups that seem to be genetically destined to low enzyme levels in adulthood.[36] The concept of gradual decrease in lactase activity after infancy would fit with the post-weaning lactase fall seen in most animal species.[31,32]

Among the possible hypotheses for explaining these differences in adult lactose tolerance are that some ethnic groups have a high incidence of diseases that damage the intestinal mucosa and inhibit lactase production. Even after affected persons have recovered and are in apparent good health, the effects may remain. If this explanation is correct, group differences in lactose tolerance would reflect differences in the incidence of such diseases.[170]

It is difficult to assess the role of disease in contributing to group differences of lactose tolerance. It is recognized that there is widespread subclinical disease of the small intestine among symptom-free and seemingly normal persons in

TABLE 3.—*Lactase Deficiency in Various Adult "Healthy" Ethnic Populations*

Ethnic Group	*Country Studied*	*No. of Subjects Studied*	*Lactase Deficient (Percent)*	*Reference*
Caucasians	U.S.A.	508	2-19	26,55,86,133-136
Caucasians	Australia	112	6-16	137,138
Caucasians	India	30	27	139
Swiss	Switzerland	17	6	56
English	England	67	22	140
Danes	Denmark	700	6	141
Finns	Finland	159	17	142
Italian 1st gen	U.S.A.	20	70	86
Greek Cypriots	England	17	88	140
Jews	Israel	354	61-67	143,144
Jews	U.S.A.	65	58-71	86,209
Arabs	Israel	67	80	145
Negroes	U.S.A.	107	70-73	132,133,135,136
Bantus	Uganda	52	90	146
Other Tribes	Uganda	63	44	146
Bantus	South Africa	38	90	148
Chinese	Australia, & U.S.A.	100	56-100	26,137,150-152
Indians	Australia, Canada, India	85	41-100	137,139,155,156
New Guinea	Australia	8	100	157
Thai	Thailand	140	100	159
Filipinos	U.S.A.	30	90	86
Japanese	Japan	35	97	161
Aborigines	Australia	44	79-90	162
Indian-Caucasian	Colombia	45	25-38	163
Chami Indian	Colombia	24	58	164
Puerto Rican	U.S.A.	28	21	165
Mexican-American	U.S.A.	50	70	86
American Indians	U.S.A.	3	67	135
Canadian Indians	Canada	30	63	166
Eskimos	Greenland	25	88	167
Eskimos-Dane	Greenland	7	13	167

various tropical countries, and that the intestinal mucosa of affected persons is altered in form and absorptive ability.[171-173] There must be, among the world's people, differences in the incidence of subclinical disease, as well as in the more severe clinical forms of disease that induce malabsorption. It is also reported that of all the disaccharidases, lactase is the most readily affected by damage to the intestinal mucosa and is the slowest to recover.[91,174,175]

A second hypothesis, namely that group differences in adult lactose tolerance are genetic in origin, is supported by an overwhelming majority of researchers in the medical and related fields.[136,140,146,149,162,173,177,181,182] Also worthy of note is the inability of other hypotheses to account for the group differences in lactose tolerance. It is difficult, for example, to conceive of an explanation other than genetic that can account so readily for the persistence of high levels of intolerance among Negroes and Orientals in the United States an environment strikingly different from those of their ancestral homelands.

Turning to more specific observations, it is relevant that various congenital disaccharide intolerances, based on enzyme deficiencies, appear to have genetic etiological factors.[17,56,79,87,90,91] It would thus not be surprising if the adult-acquired-form of lactose intolerance has a similar etiologic base. Evidence of a familial basis for primary adult lactose intolerance is also found in four studies carried out in Great Britain.[140,186-188]

Also suggestive is the evidence from three widely separated parts of the world of individuals or groups of mixed parentage whose parents or parent groups have high incidences of lactose intolerance on one side, and low incidences on the other. The mixed individuals among Greenland Eskimos,[167] and the mixed groups—Mestizos and Antioquenos in Colombia,[163] and Iru and Hutu in East Africa—[146] have incidences of intolerance intermediate between parents or parent groups.

C. *Symptomatic (secondary) syndromes*

Any disease with diffuse damage to the small intestinal mucosa also damages small intestinal

disaccharidases.[173] The activities of all these enzymes are decreased in a proportionally equal degree. The normal activity ratios of 6:2:2:1 for maltase:isomaltase:sucrase:lactase are nearly preserved. Normally the diarrhea-threshold disaccharide load is six times higher for maltose and twice higher for sucrose than for lactose. Whenever enzyme activity falls for instance to 20 percent of the normal—the diarrhea-threshold is lowered correspondingly. Expressed as absolute enzyme activity, lactase is the first enzyme to reach critically low levels. For this reason, lactose malabsorption becomes most prominent clinically. Ordinary dietary loads of maltose, and in most cases of sucrose, can still be handled despite the respective partial enzyme deficiency.

All diffuse diseases of the small intestinal mucosa are characterized by diarrhea as their major symptom. The diarrhea of disaccharide malabsorption is in these cases superimposed on an already existing diarrhea and therefore masked. Besides a symptomatic improvement, a curative effect on the underlying disorder may be observed after milk elimination in some nonspecific diarrheal diseases especially in children.

As most primary diarrheal diseases of the small intestine are transient in nature, the associated disaccharide intolerance is also transient. General disaccharide deficiencies have so far been observed in primary malabsorption syndromes (celiac disease[55,189,190] idiopathic sprue[53,55,173] and tropical sprue),[55,62,191] Whipple's disease,[192] intestinal lymphoma,[50] intestinal lymphangiectasia,[53,192] abetalipoproteinemia,[53] all with associated generalized villous atrophy. Greater variation is found in the degree of villous atrophy, frequency of occurrence, and degree of disaccharidase deficiency associated with blind loop syndrome,[53] Kwashiorkor,[193] severe malnutrition in infancy,[194] Neomycin[195] and Conovid[196] therapy, and infectious or nonspecific diarrhea in childhood (acute gastroenteritis or enterocolitis).[197-200]

It is of interest that some in this last group had normal enzyme activity on biopsy although having typical disaccharide malabsorption. Nearly all of these conditions can be treated, with subsequent return of sucrase and maltase activity to normal. In nearly half of the cases, however, lactase activity in the jejunum remains selectively and permanently deficient.[86]

D. *Chance combination of acquired lactase deficiency with other gastrointestinal disease*

Acquired intestinal deficiency, especially acquired partial lactase deficiency or the forme fruste of acquired lactose malabsorption, is very frequent among the adult population. A chance combination of pronounced or partial lactase deficiency with any other disease is therefore expected to be rather frequent. One possible reason is the increase of dietary lactose load due to the regimen prescribed by the physician for the treatment of much gastrointestinal disease. Studies show no definite increased incidence of lactase deficiency associated with peptic ulcer[58] partial gastrectomy,[58,201-206] ulcerative colitis,[207-210] regional enteritis,[210,211] irritable colon syndrome,[212-216] diverticulosis or diverticulitis of the colon,[217] infectious or nonspecific diarrhea in adults,[55] massive infestation with Giardia lamblia,[86] mucoviscidosis (cystic fibrosis of the pancreas),[218,219] infectious hepatitis,[55] and hypogammaglobulinemia.[220] After partial gastrectomy, a more rapid intestinal transit time (dumping syndrome) may be an additional factor to that of a milk-rich diet in producing symptoms of lactose malabsorption in persons with partial lactase deficiency.

Another factor to make asymptomatic partial lactase deficiency clinically manifest is its combination with inflammatory or functional disease of the large or small bowel. In persons with partial lactase deficiency, a small amount of nonabsorbed lactose reaches the colon, but this amount is not sufficient to produce diarrhea. However, when the colonic mucosa is already inflamed or irritated, the small amount of lactose may trigger diarrhea. Similarly, an inflammatory or functional disease of the small bowel with acceleration of small intestinal transit time may increase the amount of unabsorbed lactose reaching the colon sufficiently to produce diarrhea or accentuate already existing diarrhea. Partial lactase deficiency thus can become symptomatic under these conditions.

E. *Disaccharide malabsorption with intact enzyme concentration*

Total small bowel disaccharidase activity is not only reduced by a deficiency of disaccharidase concentration, but may be reduced due to an absolute or relative reduction of total absorbing surface.

Resection of at least two-thirds of the small bowel in an adult reduces total small bowel disaccharidase content sufficiently to produce disaccharide malabsorption despite normal enzyme concentration in the remaining small bowel.[84] Lactose malabsorption will be affected first and sucrose absorption next, for the same reasons as in cases with diffuse small intestinal mucosal damage resulting in general enzyme deficiency. In children small bowel resections of lesser extent may produce symptoms of lactose and perhaps of sucrose malabsorption, because the disaccharide load is proportionally much greater in children than in adults.

Newborns have several movements of soft and acid stools when breast-fed,[35,60] but only one to two formed alkaline stools when given cow's milk. The lactose content in human milk is approximately 7 percent and the lactose content of cow's milk approximately 4 percent. The daily lactose load of breast-fed newborns is astonishingly high and corresponds to 200 grams of lactose or the equivalent of 5 liters of cow's milk in adults.[28]

F. *Suggested disease associations*

Several diseases have been associated with lactase-deficient subjects more often than with lactase-normal subjects, suggesting a possible predisposing effect by the lactase deficiency. Ulcerative colitis, regional enteritis, irritable colon syndrome and osteoporosis are four such conditions. Also the increased incidence of colon carcinoma in Japanese and Africans that become Americanized has been observed.[221] Many of the lactase-deficient patients with colon carcinoma that we have studied[86] have been using milk products with varying degree of symptoms long before the carcinoma was noted. The variation in fecal bacteria reported[222] in various geographic locations might be related to the extra feeding of lactose to colon bacteria, and to the increased chronic colon disease seen among lactase-deficient subjects after they have moved to milk drinking countries.

Diagnosis

A diagnosis of disaccharide malabsorption is made only when the physician considers it in his differential diagnostic thinking. In infants and children, an evaluation for disaccharide malabsorption is indicated in every case of chronic diarrhea. In adults, an evaluation for lactose malabsorption is indicated in every case in which there is a history of milk intolerance, and in every case of intermittent diarrhea or vague abdominal symptoms, even when the dietary history given by the patient is not suggestive of milk intolerance. The absence of consistent milk ingestion or of predisposed ethnic type is also helpful in suspecting lactase deficiency. In children and adults with chronic diarrhea of known cause, associated lactose malabsorption should be searched for.

The next step is to feed the patient 50 grams of lactose in 400 ml of water. This dose corresponds approximately to the lactose content in one liter of milk.[67] In the typical case, the full array of symptoms, including massive diarrhea, will be reproduced. When no symptoms or abdominal pains occur after the 50-gram load, the test can be repeated with 100 grams of lactose. With this dose, corresponding to 2 liters of milk, the borderline deficiency patients will also experience diarrhea.[223]

For precise diagnostic purposes, the blood glucose determinations are performed at 0, 15, 30, 60, 90 and 120 minutes during the lactose tolerance test. In most normal persons, peak glucose elevations over the fasting blood glucose level occur between 30 and 90 minutes and are in the range of 21 to 62 mg per 100 ml after 50 grams of lactose. Patients with lactase deficiency show a "flat" curve, defined as a glucose rise of less than 20 mg per 100 ml for the 50-gram dose (usual range 2 to 10 mg per 100 ml) or a glucose rise of less than 25 mg per 100 ml for the 100-gram dose[76] of lactose load (usually less than 18 mg per 100 ml). During the test, subjective symptoms are noted and fecal evacuations are collected during the first 5 hours and tested with pH paper and Clinitest. The Clinitest procedure is done just as with urine testing for reducing substance. The stools in the average case contain 2 to 4 percent reducing substance. A positive test result consists of two criteria: the flat blood glucose curve, and the induction of diarrhea with a stool pH of 6 or less and having a positive Clinitest response. This combined criteria eliminates most false positive lactose tolerance tests.[67]

A new modification of the lactose tolerance test has recently been described.[224] Blood galactose is determined instead of blood glucose. Ga-

lactose, which is metabolized very rapidly, is blocked by the ethanol. The variation of the usual lactose tolerance test consists in administering orally 0.5 gram of ethanol per kilogram of body weight 10 minutes before the lactose load is fed. Serum galactose rises now to between 30 and 60 mg per 100 ml in normal adults, but only to between 0.6 to 1.8 mg per 100 ml in lactase deficiency.

A ^{14}C-lactose absorption test,[161,226] using a simple CO_2 collection apparatus, has distinguished between normal and lactase-deficient subjects. The method consists of measurement of the specific activity of $^{14}CO_2$ in the exhaled air after oral administration of 5 μCi lactose-1-^{14}C together with carrier lactose (50 grams).

Calloway,[225] using a simple hydrogen breath analysis, found a hydrogen peak 5 to 6 hours after giving a small test dose of lactose in lactase-deficient patients only. This occurred when the lactose encountered the bacteria of the colon, and the results showed excellent correlation with the lactose tolerance test. This had the advantage of giving good separation of lactase-deficient from the lactase normal persons without actually causing diarrhea.

A radiological method[125] for the diagnosis of disaccharide malabsorption has been shown to be simple and reliable. The patients were each given 4 fluid ounces (120 ml) of liquid Micropaque® barium sulphate suspension, 100 percent weight per volume, to which 25 grams of a test sugar had been added. After 60 minutes a film of the abdomen was taken with the patient supine. Other reports[227-230] all enthusiastically endorse the extremely good correlation.

The most definitive test in the diagnostic workup is the actual determination of the disaccharidase activities in the small bowel mucosa.[51] This is not necessary for the substantiation of a clinical diagnosis which has been verified by abnormal results to the disaccharide tolerance tests and normal results to the monosaccharide tests. Any of the peroral suction biopsy instruments now in use may serve this purpose. The intestinal biopsy specimen is best obtained a few inches beyond the ligament of Treitz. Absolute values for duodenal enzyme activities cannot be compared with those in the jejunum.[53-58] However, the ratios between the different disaccharidases are identical in the duodenum and in the remaining small intestine.[60,61] This permits the diagnosis of a selective enzyme deficiency even from a duodenal specimen. The sucrase to lactase ratio is usually greater than 4 to 1 in primary lactase-deficient subjects, but this ratio is not useful in secondary disaccharidase deficiency and a jejunal biopsy is required for histological and enzymatic assay.[61]

Treatment

Treatment of disaccharide malabsorption consists in the nearly complete elimination of the nontolerated sugar from the diet in infants and small children. In older children and adults, such strict measures are usually not necessary. Small disaccharide quantities are tolerated and reduction of the respective sugars is usually sufficient.

In lactose malabsorption the only nontolerated nutriment is milk. Disguised milk sources such as creams, ice creams and puddings must also be considered.[8] Lactose is not destroyed by boiling. Milk powders usually have the same lactose content as ordinary milk. Fermented milk products such as yoghurt and buttermilk contain little lactose. In commercially available yoghurt, however, fermentation is stopped before lactose is completely broken down, so that lactose content varies greatly. As butter and cheeses contain very small amounts, they are usually tolerated by most patients.

In infants, human and cow's milk have to be completely eliminated. Milk is replaced by soybean milk in newborns. Enteric-coated lactase tablets are available, but acid pH renders it nearly useless. Adults usually suffer no nutritional deficiencies on milk-free diets. In infants, calcium has to be supplied as calcium gluconate and, in older children and adults, by natural calcium sources such as cheese, nuts and spinach.

Congenital sucrose-isomaltose malabsorption poses a much more difficult feeding problem. Sucrose, our common cane sugar, is contained in so many foods that eliminating it from a diet is difficult.[8] The same applies to isomaltose, a constituent of starch and glycogen. Tolerated diets in the newborn consist of milk. Later glucose has to be added to milk instead of sucrose in formula diets. In older children the diet consists mainly of milk, meat and meat products, eggs, cheese, butter and oil and starches. Fortunately small amounts of isomaltose and sucrose are tolerated with advancing age. These tolerated amounts vary from child to child and have to be

determined empirically. Commercially available and effective sucrase*[127] (invertase) tablets may be given with meals, at a cost of about 50 cents a day, without carbohydrate restriction.

Congenital glucose-galactose malabsorption is the most difficult feeding problem. Fructose is the only carbohydrate tolerated in this disorder. The small amounts of fructose contained in certain fruits and vegetables are insufficient as carbohydrate source. Galactose is easily avoided by the elimination of lactose—that is, milk. Glucose, however, forms part of all common disaccharides and polysaccharides in human nutrition, and all have to be completely eliminated. The only exception is inulin, which is formed of fructose. Inulin is present instead of starch in Helianthus tuberosus, variously called topinambour, earth apple, Canada potato, Jerusalem artichoke or tuberous sunflower.[8] This vegetable serves as the main carbohydrate source and is fed together with the usual protein and fat sources.

In all kinds of primary diarrheal disorders of children and adults, elimination of milk should be attempted temporarily for two or three weeks. Often symptomatic improvement is noted. In smaller children additional temporary elimination of sucrose may occasionally be helpful too. When the primary diarrheal disorder is cured, milk and sucrose are again tolerated in most cases.

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PROCEDURES FOR THERAPEUTIC ABORTION

If the patient is under 12 weeks pregnant, suction curettage is the method of choice [for therapeutic abortion]. This, you may remember, was originally introduced into this country after a series of nearly 67,000 suction curettages was reported in Czechoslovakia without a single fatality. After 12 weeks the feeling is that the patient should be allowed to go to 14 weeks; she then has enough amniotic fluid to be tapped by a transabdominal amniocentesis. A total of 100 to 200 ml of amniotic fluid is drawn off and replaced by an equal amount of 23.1 percent sodium chloride solution. These patients behave in a very admirable fashion. The lag period between the saline amniocentesis and actual expulsion of the fetus will vary from one to seven days. In our experience we have had to repeat the saline amniocentesis in three different patients. On the second time around, all three patients delivered without problem. Two retained placentas have been removed in the delivery room. Otherwise the patients deliver very quietly in bed under twilight sleep.

We have found that these patients, if they are admitted to the hospital, should be scattered throughout the entire hospital population. When they are segregated, as they originally were in Hawaii, the unit quickly gets labelled a leper's colony and is treated as such.

—ROBERT N. RUTHERFORD, M.D., Seattle
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